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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/078,768	06/16/1993	RICHARD H. TULLIS	PMB9658	9155

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EXAMINER	
MARTINELL, JAMES	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/078,768	TULLIS, RICHARD H.	
	Examiner	Art Unit	
	James Martinell	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 71 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,023,243. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1 of U.S. Patent No. 5,023,243 is a specific embodiment of the generic method of claim 71 in the instant application. Applicant indicates (paper no. 80, page 25) that he disagrees with this rejection and will address the merits of the rejection upon an indication of allowable subject matter. There is no provision for holding a rejection in abeyance. Thus, in order for any response to this Office action to be considered a complete response, applicant must either: (1) argue the merits of the rejection, (2) offer to submit a proper Terminal Disclaimer, or (3) file a proper Terminal Disclaimer.

Claims 75-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims include new matter as outlined below.

(a) There is no basis in the application as filed for "introducing said synthetic oligonucleotide into the cell at a temperature between 0° and 80°C to hybridize said synthetic oligonucleotide to the subsequence of the messenger ribonucleic acid" (claim 75). The application does not disclose an *in vivo* method at 80°C.

This rejection is repeated for reasons already of record (*e.g.*, Office action mailed September 10, 2002, page 3, item (f)). Applicant's argument (paper no. 80, page 8) is not convincing because the section of the instant application from page 13, line 3 through page 15, line 4 deals with *in vitro* testing of mRNAs for hybridization to oligonucleotides and not with *in vivo* downregulation of protein synthesis. The disclosure of *in vivo* testing begins at page 15, line 5.

Claims 64-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited to the preparation of stabilized forms of oligodeoxyribonucleotides that are phophotriesters, does not reasonably provide enablement for all stabilized forms of oligodeoxyribonucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection is repeated for all of the reasons given in the Office action mailed September 10, 2002 (pages 2-173-20).

Applicant asserts (paper no. 80, paragraph bridging pages 10-11) that the instant application contemplates, enables, and claims the use of *in vivo* antisense using double stranded oligomers. This assertion is not convincing because the instant application does not disclose the use of double stranded antisense agents. The application throughout refers to the "hybridization" of the antisense agent to its target. The term "hybridization" refers to the formation of a double stranded nucleic acid by annealing of two single stranded molecules (see Stenesh, page 226, definition number 1 for "hybridization"). For a double stranded antisense agent to work, a triplex would need to be formed. The instant application does not disclose the formation of triplexes.

The Declaration (executed June 14, 2002) by Dr. Crooke is not persuasive for the following reasons.

(a) Section 3, last paragraph is not persuasive because it relates an opinion only. No actual search query or search results are disclosed, nor there established what

would be a reasonable or likely search query by one of skill in the art as of the effective filing date (October 23, 1981).

(b) In section 5a the issue is misrepresented. The record contains no comment from the examiner as to the "inventive principle" regarding selection of the form of stabilized oligonucleotide to be used. The "point of novelty" is irrelevant in relation to a rejection under 35 U.S.C. § 112, first paragraph. The targeting of the coding region is not at issue in this application.

(c) Regarding section 5b, declarant's comments in connection with what one of skill in the art would have been led to based on the mere reference to Miller et al in the application (Biochemistry 16: 1988 (1977)) and what Miller et al (1977) in turn refers to, can be speculation at best and is for that reason most unpersuasive. It is noted that declarant points to no statement in the application as filed that would lead one of skill in the art to use any of the referenced material in Miller et al (1977). Indeed, Miller et al (1977) is not even incorporated by reference in the instant application. Reading the context in which Miller et al (1977) is used (see the instant application at page 17, lines 21-25), it is not understood why one of skill in the art would look to Miller et al (1977) (let alone a reference (Eckstein et al, Angew. Chem., Int. Ed. Engl. 6: 949 (1967)) referred to by a work referenced (Miller et al, Biochemistry 13: 4888 (1974)) by Miller et al (1977)) for some form of modified oligonucleotides other than the phosphotriesters that Miller et al (1977) discloses and that the application points to Miller et al (1977) for. Declarant's statements regarding a "routine search" of the literature is not persuasive because it is the application that is to be enabling, not further searching and extrapolation by those of skill in the art. Furthermore, it has not been established in this record that all of the

stabilized forms of oligonucleotides that are disclosed in the prior art actually work *in vivo*.

(d) In section 5b at page 6 declarant states "application provides adequate guidance as to which stabilized oligonucleotides to use in the invention". This assertion is most unpersuasive in the absence of an indication as to where the instant application provides such a teaching. The only disclosure regarding this is the reference to Miller et al (Biochemistry 16: 1988 (1977)) at page 17 21-24 and this reference is to the production of phosphotriesters. A patent to a method of oligonucleotide directed inhibition of expression using phosphotriesters has already been issued to applicant (Tullis U.S. Patent No. 5,023,243). Additionally, implied in this statement (section 5b, page 6) is that not all stabilized oligonucleotides ought to be used in the invention. If that is the case, then the application as filed is deficient in not proving guidance to those of skill in the art as to which stabilized forms to use. That others had synthesized some forms of oligonucleotides (see the references cited in section 5b) does not convince that the application teaches or points one of skill in the art to the potential use of those forms of modified oligonucleotides in the claimed methods.

(e) In section 6a declarant states, "the stabilized oligonucleotide is simply administered" yet there is no teaching of how to administer any of the oligonucleotides.

(f) Section 6b deals with uptake of oligonucleotides in culture, but that is not an issue here. Applicant already has a patent that claims that subject matter (Tullis U.S. Patent No. 5,919,619).

(g) In section 6b, page 7, declarant's *ad hominem* remarks in connection with Gura (Science 270: 575 (1995)) are given no weight. Declarant has demonstrated no

competence in regard to whom Gura did or did not interview for the Science article. Declarant has not gainsaid the substance of the Gura article.

(h) Declarant's arguments in section 6b, pages 7-8 are most unconvincing. Of the four articles mentioned in that section, only two are of record (Mercola et al and Putnam et al). The arguments related to Mercola et al are not convincing because all of the references cited by Mercola et al were published long after the effective filing date of the instant application. For example, declarant makes much of the references cited by Mercola et al at pages 54-55, yet none of those references was published prior to 1992 (all were published in 1992, 1993, or 1994). Similarly the references cited by Putnam on pages 154 and 156 (pointed to by declarant) were published in 1993 and 1994. Declarant and applicant have not established for this record whether any of the methods used in either of the references in the record or those referred to by those references (this method of second-hand citation of references to provide evidence is of little value in establishing fact) are comparable to anything taught or disclosed in the instant application. Accordingly, these arguments are not convincing. Declarant also discusses Hijiya et al (Proc. Natl. Acad. Sci. USA 91: 4499 (1994)). Declarant discusses Hijiya et al to teach the inhibition of the MYB gene *in vivo* in mice by the use of oligonucleotides. This is in fact disclosed in the reference, however, the reference does not include certain details such as the length of the oligonucleotides used, the number of different oligonucleotides that may have been used, and whether the oligonucleotides used were complementary to the coding region of the MYB gene. Additionally, Hijiya et al concludes (page 4503, last paragraph of the text):

> Knowledge concerning DNA uptake mechanisms, intracellular ODN [oligodeoxyribonucleotide] trafficking, mRNA disruption mechanisms, and, of equal importance, how apparent resistance develops will all

> contribute significantly to the effective pharmaceutical use of these compounds. Accordingly, while this area remains in its scientific infancy, the *in vivo* studies and those of our colleagues . . . convince us that modulation of gene expression with antisense DNA is a therapeutic strategy worth pursuing.

If the science of antisense inhibition of expression *in vivo* was in its infancy in 1994, one is left to wonder what the state of the art was in 1981. Hijiya et al also echoes the issues that have been long standing in this application, *viz.* uptake, intracellular trafficking [degradation], and interactions with target mRNA [specificity of hybridization] (see page 4500, right hand column and page 4503, last paragraph of text). Hijiya et al (and Gura? and Rojanasakul (Adv. Drug Delivery Rev. 18: 115 (1996))?) are not alone since Mercola et al (Cancer Gene Therapy 2 (1), 47-59 (1995)) at page 54 in a discussion of oligonucleotide delivery *in vivo* says:

> Are oligodeoxynucleotides a feasible means of delivering an antisense-based compound and is there concordance between the results for antisense oligodeoxynucleotides and plasmid-derived antisense RNA? Human and animal trials of oligodeoxynucleotides are in their infancy and comparisons among approaches are sparse, however, several signposts are available.

Again, the science is in its infancy, but now in 1995.

(i) Section 6c is not persuasive because declarant does not establish all modified oligonucleotides to be stable *in vivo*. That some are stable is not at issue. The question is what the application as filed teaches one of skill in the art in connection with which stable forms of oligonucleotides are available and which will operate as claimed. It is noted that declarant mentioned, but did not discuss how Rojanasakul was used in the rejection.

(j) In section 6c declarant claims that the examiner "relies on Gura to support his contention that stabilized oligonucleotides do not hybridize". This is simply incorrect. The issue is what the application teaches what effect the stabilization

of oligonucleotides has on the specificity of hybridization (a difficulty with the method that is brought out by both Gura and Rojanasakul and now Hijiya et al). It is the examiner's position that the application does not provide adequate guidance for one of skill in the art to practice the claimed invention in its full scope without resorting to undue experimentation for reasons that have been discussed at length in this record.

(k) It is noted that declarant did not address the issue of the breadth of claims 62-70 and 72 in that these claims embrace a method that does not require the use of stabilized oligonucleotides at all.

Applicant's arguments (paper no. 73) are not convincing for the following reasons.

Applicant asserts (pages 7-8) that the statements of Dr. Crooke must be accepted as true in the absence of facts to the contrary. An analysis of Dr. Crooke's declaration is contained hereinabove.

Applicant cites the factors outlined by the U.S. Court of Appeals for the Federal Circuit (*In re* Wands (8 USPQ2d 1400, Fed. Cir. 1988)). They are listed here in the order that applicant stated them.

Wands Factor 8 (the breadth of the claims): The first factor involves the breadth of the claims. It is noted here that all of the claims are drawn to a method of inhibiting the production (*i.e.* downregulating) of a protein without inhibiting the expression of other proteins *in vivo*. For the record, here *in vivo* means in a living organism and not inside living cells in culture. In some of the scientific literature, the term *in vivo* may be used to describe a process in living cells in culture conditions. That is not the case here. The term *in vitro* may be used to describe processes in living cells in culture or processes in a cell-free environment. The meanings of these terms are usually clear when taken in context within a given document. The instant application uses the term *in vivo* to describe both the use of the method in an organism and in cells in culture (*e.g.*, see Example 1 beginning on page 12 of the instant application). For purposes of this Office action, the terms are used thusly: "*in vivo*" means in an organism, "*in vitro*" means in a cell-free system, "in cell in culture" means in cells grown outside of a

complete organism on some sort of artificial medium. The requirement for the claims to selectively inhibit the expression of a single protein *in vivo* without inhibiting the expression of other proteins needs to be kept in mind when considering any of applicant's arguments.

Wands Factor 4 (the nature of the invention): This is an invention that is carried out inside a living organism, a self-evidently complex system.

Wands Factor 5 (the state of the prior art): Applicant argues in connection with this factor at length and assert that the state of the prior art provides for the availability of stabilized oligonucleotides, teaches that oligonucleotides are taken up by cells *in vivo*, and that evidence exists in the prior art to indicate that stabilized forms of oligonucleotides will specifically hybridize to mRNAs *in vivo*.

Wands Factor 6 (the level of one of ordinary (sic) skill, the court listed this as "the relative skill of those in the art"): The relative skill of those in this art is certainly high. Applicant argues that one of skill in the art would have been aware of several forms of stabilized oligonucleotides by searching the literature and by referring to references referred to by a reference referred to in the application.

Wands Factor 7 (the level of predictability in the art, the court listed this as "the predictability or unpredictability of the art): Applicant argues that the art is predictable and alludes to publications filed after the effective filing date of the instant application (*i.e.* October 23, 1981) and declarations already in this record (by Drs., Schwartz, Ruth, and Crooke) to support the notion of predictability in the art of specific *in vivo* antisense inhibition of protein synthesis.

Wands Factor 2 (the amount of direction provided by the inventor, the court listed this as "the amount of direction or guidance presented"): Applicant argues that the application refers to enough for one of skill in the art to be able to practice the claimed invention without performing undue experimentation but does not point to much in the application itself that may guide or direct one of skill in the art in the practice of the claimed invention.

Wands Factor 3 (the existence of working examples, the court listed this as "the presence or absence of working examples): Applicant points to working examples that include the use of

phosphotriesters oligonucleotides as antisense agents in cells in culture (*i.e. in vitro*). Applicant has two U.S. Patents (5,023,243 and 5,919,619) that already claim these aspects of the invention.

Wands Factor 1 (the quantity of experimentation needed to make or use the invention): Applicant argues at length that no undue experimentation is necessary for one of skill in the art to practice the claimed invention. The arguments are accompanied by declarations and post-effective-filing-date publications.

Applicant asserts (page 9) that one of skill in the art would be able to practice the claimed invention using the application as a guide. These arguments are most unconvincing as explained below.

Applicant asserts that the application provides adequate guidance for one of skill in the art to use any form of stabilized (against degradation by nucleases) oligonucleotide in the claimed invention. Applicant asserts (pages 10-12) that the application even supports the use of unmodified oligonucleotides (*i.e.* the phosphodiester form) *in vivo*. Applicant had previously argued (paper no. 33, section C) that the examiner misinterpreted a statement made by the inventor during the prosecution history of a prior application. Applicant's argument is unconvincing in the face of the simple, direct, and unambiguous language used by the inventor. Applicant's arguments are further unconvincing in view of published statements under the name of the inventor and others. For example, in the publication by Tullis et al (Biotechnology International, 1992, reference A15, already of record) state on page 79 that one of the key events in the development of antisense technology was the development was more efficient systems for the synthesis of normal and phosphorous modified oligodeoxyribonucleotides and then goes on to cite a number of references, all of which were published subsequent to the effective filing date of the instant application. (The Beaucage and Caruthers reference is listed as being published in 1980 at page 79, but is listed as published in 1984 in the bibliography. The 1984 date is almost certainly correct because the Beaucage and Caruthers reference is a European Patent application that was filed in 1982.Additionally, at page 80 (top part of the right hand column), Tullis et al mention problems with uptake and stability of unmodified oligonucleotides and give no clue to the reader to do any of the things that applicant now asserts would have been obvious to anyone of skill in the art in 1981. Thus, the evidence in the record

indicates that applicant himself did not know that unmodified oligonucleotides could be used as antisense agents even as late as 1992. The most recent response (paper no. 73 and its accompanying declaration) does not mention the statements of Tullis. Applicant's argument citing Example 1 as basis for the use of the claimed method utilizing unmodified oligonucleotides (paper no. 73, page 11) is not convincing because Example 1 is limited to the use of the method in cells in culture. Thus, the remarks of Tullis stating that, "Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down *in vivo* before having the desired effect" are still relevant (the method of Zamecnik and Stephenson uses unmodified oligonucleotides as antisense agents in cells in culture). There is no evidence in the record to show that applicant disclosed or conceived of the use of unmodified oligonucleotides as antisense agents as of the effective filing date of the instant application.

Applicant further argues that the application need not teach what is known in the art (paper no. 73, pages 12-16). This is correct; however, the application not only does not teach what was not known in the art, but a number of post-effective-filing-date references in this record show that much was not known about this art and that much experimentation was needed to make the claimed method work even more than a decade after the effective filing date of the application. Applicant asserts that phosphotriester oligonucleotides are simply a representative example of the stabilized oligonucleotides (paper no. 73, page 13). This assertion is not persuasive because the phosphotriester oligonucleotides are the only disclosed example of stabilized oligonucleotides in the application. There is no disclosure of any other particular form of stabilized oligonucleotide, nor is there a hint of how the stabilized form may affect the specificity of hybridization *in vivo*, a crucial aspect for the proper operation of the claimed invention. In a review by Crooke (Bio/Technology 10: 885 (August 1992)), it is stated (page 885) that,

> Methylphosphonates appear to have lower therapeutic indexes. Too few data are available to draw conclusions about other classes of oligonucleotides. . . . Very few data support putative mechanisms of action, and generalizations concerning desired mechanisms of action are not possible. Nevertheless, a variety of mechanisms of action may be employed by oligonucleotides to result in significant biological activities.

Thus, even nearly eleven years after the effective filing date of the instant application, it was not possible for those of skill n this art to make generalizations concerning the mechanisms of action of oligonucleotides. That being so, how can the instant application be said to fairly teach those of skill in the art how to practice the full breadth of the claims? It is noted here that the instant disclosure had been published as WO 83/01451 on April 28, 1983 and so the method of applicant was available to those of skill in the art at least as early as that date. Applicant further argues (paper no. 73, page 14) that the application "points to additional references describing a number of stabilized oligonucleotides available at the time of filing". This is an overstatement because the application itself refers to one reference that discloses the use of phosphotriesters (Miller et al, Biochemistry 16: 1988 (1977)) which in turn refers to a second reference dealing with phosphotriesters (Miller et al, Biochemistry 13: 4888 (1974), which in turn refers to Eckstein et al (Angew. Chem., Int. Ed. Engl. 6: 949 (1967)). This chain of referencing is discussed in the Crooke declaration (item 6) without giving any reason why or how one of skill in the art would be lead to Eckstein et al and why one of skill in the art would combine Eckstein et al with the instant application (if Eckstein et al were so closely connected to the instant invention, it is not clear why Eckstein et al was not directly cited in the application itself). Both Miller et al references refer to a number of other works, so it is unclear why this one would appear so important to one of skill in the art. Neither the Crooke declaration, nor applicant's arguments in paper no. 73 point to any context in Miller et al (1977) that would lead one of skill in the art to Miller et al (1974) or any context in Miller et al (1974) that would lead one of skill in the art to Eckstein et al. Applicant goes on to assert that one of skill in the art would run literature searches to find more forms of stabilized oligonucleotides that might be suitable for use in the claimed method (paper no. 73, pages 14-15). This argument is not convincing because the record does not contain an example of a plausible search or the results of such a search. Additionally, it is the application that is to teach one of skill in the art how to make and use the invention. In view of the difficulty that others have encountered in getting methods embraced by the claims to work (the earliest published account being in 1992), it is evident that those of skill in the art did in fact need to perform undue experimentation (it was and is an active field of research with many highly skilled artisans

and a great amount of resources) to get the claimed invention to work. The application is, at best, an invitation to experiment.

Applicant argues that the examiner is to consider patentability of the claimed invention in view of the record as a whole (paper no. 73, pages 16-19). This has been done. The discussion of the Crooke declaration (see above) is incorporated here, as is the discussion of the declarations of Ruth and Schwartz (see the Office action mailed December 17, 2001).

Applicant argues that the instant application enables the use of oligonucleotides *in vivo* (paper no. 73, pages 19-32 and dismisses the various pitfalls and demonstrated (as published) difficulties in achieving antisense inhibition of expression of a specific polypeptide *in vivo* as being solved by routine experimentation. These arguments are most unconvincing. First, there is no "implied assertion" (leaving aside the impossibility of an *implied* assertion, something is either asserted or implied or perhaps inferred) in the record regarding any requirement that every embodiment of the invention be disclosed or taught (see paper no. 73, pages 19-20). There is in fact no method of *in vivo* antisense use taught in the application. Rather, what is described is a goal, not a method *per se*. The examiner understands that some experimentation may be necessary to practice a claimed invention and such routine experimentation shall not impede patentability. What the instant claims require of those of skill in the art is undue experimentation. Applicant again points to the phosphotriester example in the instant application (paper no. 73, page 2). It is reiterated that applicant already has a patent that covers the use of phosphotriester oligonucleotides as antisense agents. Applicant then asserts (paper no. 73, page 20) that "no more than routine experimentation is required to determine which oligonucleotides work in the invention in view of the examples provided in the application". This assertion is not convincing in view of the discussion in the previous Office actions (mailed December 17, 2001 and September 10, 2002) and hereinabove and in view of what is disclosed in Branch (TIBS 23: 45 (February 1998). Branch confirms and echoes some of the difficulties with the method as outlined in Rojanasakul and Gura as discussed in the Office action mailed December 17, 2001. The following quotes are from Branch.

they [antisense molecules] are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven. Furthermore, a wide variety of unexpected non-antisense effects have come to light. (Abstract)

when an antisense molecule causes a biological effect, it can be extremely difficult to determine whether the change occurred because the reagent interacted specifically with its target RNA, or because some non-antisense reaction - - involving other nucleic acids or proteins - - was set in motion. (page 46, right hand column)

quantitative data about the magnitude of antisense-induced side reactions are limited, (page 47, left hand column)

An antisense molecule is typically taken to be 'specific' if two criteria are met: (1) there is no gross loss of cell viability, and (2) the levels of the target RNA and its associated protein fall much more than those of the control RNAs. However, this type of experimental design is too limited in scope to provide information about global changes in the RNA and protein populations. (page 47, left hand column)

So far, the concept that an antisense molecule can selectively knock out a single gene appears to have been untested. In the future, several techniques, in addition to two-dimensional gel electrophoresis, might be employed to investigate antisense specificity. (page 47, center column)

The ratio of intended to unintended hits will depend on a complex and unpredictable combination of factors that determine whether the antisense molecule and the potential targets co-localize and whether the complementary sites in the RNAs are buried under proteins or are involved in intramolecular bonds that make them inaccessible. (page 48, center column)

Because it is very difficult to predict what portions of an mRNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells. (page 49, left hand column)

Since accessibility cannot be predicted, rational design of antisense molecules is not possible. (page 49, center column)

The relationship between accessibility to ODN [oligodeoxynucleotide] binding *in vitro* and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored, and will continue to be an active area of research in the future. It is not yet clear whether *in vitro* screening techniques of the sort used by Milner and co-workers [Milner et al, Nat. Biotechnol. 15: 537 (1997)] will identify ODNs that are effective *in vivo*. (page 49, right hand column)

These passages speak for themselves and run counter to applicant's assertions that "nothing beyond routine experimentation was required to administer the antisense oligonucleotides under *in vivo* conditions and detect a downregulation in the expression of a specific protein" (Schwartz and Ruth declarations quoted in paper no. 73, page 20). Likewise, the Crooke declaration (item 6a) is at odds with the Branch article in stating

> Nothing more than routine experimentation was necessary to use the stabilized oligonucleotides known in the art in October 1981 in the invention. The methods for using different stabilized oligonucleotides according to the invention are essentially identical to the methods for using phosphotriester oligonucleotides set forth in the application. The stabilized oligonucleotide is simply administered, and the expression of the target protein is monitored. This experimentation was routine for one of ordinary skill in the art in 1981.

The Branch quotations above indicate that such monitoring cannot be used as an indicator of downregulation of expression of a single protein *in vivo*.

Applicant asserts that the examiner "seems to require that Applicant have performed the testing necessary for FDA approval in order to satisfy the enablement requirement." The examiner has not used the term "FDA" or "Food and Drug Administration" in this record at all not even one time (except of course for here). The examiner has made no such requirement, implies no such requirement, does not implicitly assert that any such requirement exists for patentability, and shall not make any such requirement. Therefore, applicant's remarks (paper no. 73, page 21) in response to the perceived requirement are given no weight at all.

Applicant argues that the specification provides adequate guidance regarding cellular uptake of oligonucleotides *in vivo* (paper no. 73, pages 21—25). Applicant cites Summerton (J. theor. Biol. 78: 77 (1979)) to disclose the uptake of both RNA and DNA by animal cells, yet at page 84 Summerton reports,

> Double-stranded DNA is also taken up readily with newly-taken-up homologous DNA remaining undegraded substantially longer than heterologous DNA. Single-stranded DNA is generally reported not to be taken up or to be taken up much slower than double-stranded DNA.

Since single-stranded oligonucleotides are required for the instant claims (double-stranded oligonucleotides will not work because they are not free to hybridize to the target mRNA) the problem of uptake remains. Applicant also cites Zamecnik and Stephenson (1979) to support the notion of cellular uptake of oligonucleotides being well known. However, Zamecnik and Stephenson (1979) deals with cells *in vitro* (*i.e.* in cell culture conditions) and not *in vivo* (*i.e.* in an organism). A U.S. Patent to methods of antisense inhibition of protein expression in cells in culture has been issued to applicant. Applicant has provided no data to show the equivalence of uptake of oligonucleotides in cells in culture to be the same as or similar to the uptake of oligonucleotides *in vivo*. Applicant complains that the examiner has not given reasons for a conclusion of a lack of correlation for an *in vitro* (cell culture) or *in vivo* animal model (paper no. 73, page 22). This is incorrect. Rojanasakul has long been cited by the examiner in this record as supporting the idea that *in vivo* antisense methods are plagued by such problems as: uptake, degradation, and specificity. That results in cell culture conditions cannot be translated to *in vivo* systems is seen in Rojanasakul at, for example page 118.

3. Can antisense work in living systems?

> There are numerous studies demonstrating the effectiveness of antisense ONs [oligonucleotides] in various cell culture systems. However, several key questions remain, the most obvious one being "Can the antisense approach work in vivo?". This question has often been posed in different forms depending on the background of the person asking the question. From a drug delivery standpoint, the key question is often addressed like "How can antisense ONs be targeted to diseased cells, sparing normal cells?" or "How can antisense ONs be effectively delivered into the intracellular target sites where they can then exert their action?". The first question may be readily answered with the following postulate. If the antisense ONs exhibit no cellular toxicity or non-specific antisense activity, then targeting at the cellular level would not be necessary; that is, all cells could be exposed to antisense ONs. In principle, the exquisite specificity of antisense ONs implies that these compounds are less likely to cause toxic side effects in comparison to conventional drugs. However, several recent studies appear to suggest that cellular toxicity and non-specific activity of antisense ONs can occur (albeit in cell culture systems). . . . To demonstrate antisense activity, ONs that are not complementary to the target RNA are usually used as controls. An antisense activity is implicated if the antisense ON inhibits better than the controls. However, frequently the control ONs inhibit as well or better than the antisense ON . . . . Non-specific toxicity of antisense ONs has also been

> suggested as a result of their degradative products in different cell types, particularly the hematopoietic cells. . . .
>
> The second question "How can antisense ONs be effectively delivered into cells?" is equally difficult to answer. Most antisense ONs are poorly taken up by cells due to their hydrophilic nature and large molecular structure. In many cases, biological antisense activity can only be achieved in the presence of transfer vectors such as cationic lipids and liposomes. The obviousness of this problem, however, does not necessarily diminish the potential use of ONs in vivo, and there are few examples of successful in vivo treatment in the absence of specialized delivery systems [44, [Wickstrom et al, Cancer Res. 52: 6741 (1992)], 45 [Kitajima et al, Science 258: 1792 (1992)]]. Much effort has been made with some success to chemically modify ON and to develop carrier vectors for effective delivery of antisense ONs.

Were applicant's arguments correct, section 3 of the Rojanasakul article would be unnecessary. The article by Gura echoes what Rojanasakul reports. Applicant's *ad hominem* criticisms of Gura are given no weight as explained hereinabove in connection with the Crooke declaration. Applicant goes on (paper no. 73, pages 23-24) to use Gura to support the notion that the claimed invention is enabled using mathematical values from *In re* Wands (8 USPQ2d 1400, Fed. Cir. 1988). Applicant points out that in *Wands* 4 of 143 (2.8%) hybridomas successfully produced monoclonal antibodies. This much is correct. Applicant then uses the report in Rojanasakul that 1-2% of oligonucleotides administered to cells in culture become cell-associated. This much is correct too. Applicant then somehow concludes that *Wands* along with Gura and Rojanasakul weighs in favor of enablement. This conclusion is inexplicable. What *Wands* deals with is a success rate of 2.8%, *i.e.* 2.8% of hybridomas produced were 100% successful in producing the monoclonal antibodies that were the subject of the invention. The court found that this was an acceptable success rate to support enablement. Applicant has not pointed to any success rate at all and somehow considers the 1-2% "cell-association" (not necessarily cellular entry) of oligonucleotides in cells in culture, with no report of any success of the claimed method at all *in vivo,* to be close enough to the 2.8% success rate in *Wands* to pass the enablement test. Such rough and unwarranted equivalency of similar percentages of such dissimilar molecules involved in such incomparable biological processes and in such unlike states (*i.e.* rate of cell-association compared to success rate of monoclonal antibody production) cannot blindly be translated from one situation to

another. There is no magic *Wands* percentage threshold to prove enablement. Applicant misquotes Rojanasakul as stating there are "examples of successful in vivo treatment in the absence of specialized delivery systems." The complete and correct quote runs this way:

> The obviousness of this problem, however, does not necessarily diminish the potential use of ONs in vivo, and there are few examples of successful in vivo treatment in the absence of specialized delivery systems [44, [Wickstrom et al, Cancer Res. 52: 6741 (1992)], 45 [Kitajima et al, Science 258: 1792 (1992)]].

The "few" successful examples cited by Rojanasakul were published in 1992, more than ten years after the effective filing date of the instant application. The sense given in Rojanasakul is directed at the potential of *in vivo* antisense (indeed, Rojanasakul uses the term "potential") as of 1996 rather than the notion that antisense methods had had an established use as early as 1981 (the effective filing date of the instant application). Indeed, the review article by Crooke et al (Annu. Rev. Pharmacol. Toxicol. 36: 107 (1996)) in Table 2, page 116 reports the earliest results of the use of antisense oligonucleotides in animal models to be in 1989 (Kulka et al, Proc. Natl. Acad. Sci. USA 86: 6868 (1989)) with all other reports coming in 1991 to 1995. Additionally, applicant cites Phillips et al (1994), Mercola et al (1995), Putnam et al (1996), and Hijiya et al (1994) (paper no. 73, pages 24-25) as supporting enablement, but applicant establishes no connection between the actual methods used in any of these references and what is taught in the instant application. Additionally, each of these references was published more than a decade following the effective filing date. It is again noted that Hijiya et al, cited by applicant to support the position that the instant application is enabled, characterizes this art as one that "remains in its scientific infancy" as late as 1994:

> Knowledge concerning DNA uptake mechanisms, intracellular ODN [oligodeoxyribonucleotide] trafficking, mRNA disruption mechanisms, and, of equal importance, how apparent resistance develops will all contribute significantly to the effective pharmaceutical use of these compounds. Accordingly, while this area remains in its scientific infancy, the *in vivo* studies and those of our colleagues . . . convince us that modulation of gene expression with antisense DNA is a therapeutic strategy worth pursuing.

Thus, the published evidence in this record indicates that even though the method of Tullis was published in 1983, it was several years before highly skilled artisans in an active area of research published any result of success in getting the method to work. This evidence weighs heavily against the idea that the instant application provides enough guidance for one of skill in the art to practice the claimed invention as early as the effective filing date of the instant application.

Applicant then argues the issue of *in vivo* stability of the antisense oligonucleotides to be administered (paper no. 73, pages 25-28). The statements of Tullis referred to above speak against the workability of the method *in vivo* by the "just add more" method now advocated by applicant. There is no disclosure of the use of unmodified oligonucleotides *in vivo* nor is there any evidence that the inventor contemplated the use of unmodified oligonucleotides *in vivo*. The discussion of the post-filing-date remarks of Tullis et al and Tullis hereinabove are incorporated here. Likewise, the discussion of the use of stabilized oligonucleotides other than phosphotriesters hereinabove is incorporated here. Applicant's argument in connection with Rojanasakul (paper no. 73, page 27) are most unconvincing because the part of Rojanasakul alluded to and applicant's argument are in connection with the use of the method on cells in culture. The issue is directed to the use of the method *in vivo*. Applicant already has an issued U.S. Patent (5,919,619) that claims the method used on cells in culture. The discussions of Gura hereinabove are incorporated here. Additionally, applicant's argument in connection with Gura (paper no. 73, pages 27-28) is most unconvincing because although Gura reports that some biological effects are seen upon administration of oligonucleotides, Gura goes on to explain that the oligonucleotides do not always work by the expected mechanism (*i.e.* the mechanism disclosed in the instant application) and that it is difficult to tell what mechanism causes the biological effect. This idea is corroborated by Branch. Applicants' arguments in connection with the examiner failing to carry the burden of showing that cell culture systems cannot be compared to *in vivo* systems (paper no. 73, page 28) are not convincing for the reasons given hereinabove in connection with the issue of cellular uptake of oligonucleotides.

Applicant argues (paper no. 73, pages 29-32) that the instant specification provides adequate guidance in connection with the specificity of *in vivo* hybridization of oligonucleotides. Applicant's argument regarding the number of random combinations in a genome are not relevant to the basis of the rejection because the rejection is based upon the potential effect of changing the backbone of the oligonucleotides from a phosphodiester backbone to some other type of backbone to achieve increased stability of the oligonucleotides upon specificity of hybridization. That this was not only a concern among those of skill in the art, but was incompletely understood even as late as 1988 (Rojanasakul reference number 54, Stein et al, Gene 72: 333 (1988)) is evidenced by Rojanasakul (*e.g.*, page 119 "these [phosphorothioate] compounds, when compared to their unmodified counterparts, tend to have lower binding affinity to their target sequences due, possibly, to diastereomer formation [54]."). Applicant's arguments in connection with Summerton (1979) are most unconvincing (paper no. 73, pages 29-30). Applicant asserts that double-stranded oligonucleotides are available for the method of the instant application, yet applicant provides no evidence for this conclusion. There is no hint in the application that double-stranded oligonucleotides will work in the claimed method. In fact, the purported mechanism of action disclosed in the instant application would preclude one of skill in the art from considering the use of double stranded oligonucleotides because such molecules are not free to bind with the target mRNA without the two strands first being separated. The application does not hint at how such strand separation is to be achieved after *in vivo* administration of the double-stranded oligonucleotide. The discussions of Gura, Rojanasakul, Phillips et al, Hijiya et al, Mercola et al, and Putnam hereinabove are incorporated here. None of these references suggests that as of the effective filing date of the instant application, one of skill in the art would know that changes in the backbone of oligonucleotides would not affect specificity of hybridization *in vivo*. Additionally, Branch reports that many non-specific effects result upon administration of oligonucleotides both on cells in culture and *in vivo*.

The declaration by Dr. Hecht filed March 7, 2003 has been considered. This declaration is not persuasive for the following reasons.

(a) Declarant characterizes each of the Gura, Rojanasakul, and Hijiya et al references narrowly as being directed toward the "immediate clinical applicability of *in vivo* use of antisense technology" (section 5 of the declaration). This characterization is unduly narrow since these references all address the broader issues of uptake, stability, and specificity of hybridization of the antisense agent to its intended target (*e.g.*, see the summary under the title in Gura, sections 3 and 4 of Rojanasakul, and the last paragraph of text on page 4503 of Hijiya et al. Declarant's arguments in connection with potential toxic effects of antisense agents are irrelevant because the rejection is not based on the existence of potential toxic effects, but is based on the lack of an adequate in the instant application as to how to practice the claimed invention *in vivo*. Declarant makes o correlation between any of the work described in the published literature and the disclosure in the instant application. Declarant asserts (page 6, first full paragraph that "successes achieved in the field of antisense technology have been witnessed, thereby ratifying the views of proponents of antisense at the time of the invention and silencing, indeed converting, many critics to what is clearly the correct view: antisense works *in vivo* as taught by the present application." Declarant does not support this assertion with any named critic who has been either "silenced" or "converted" and does not make any correlation or connection between any successful *in vivo* antisense trial and any *in vivo* antisense method disclosed in the instant application. Without such connections, no number of citations of successful *in vivo* antisense trials published subsequent to applicant's effective filing date can support the notion that the instant application provides an enabling disclosure within the meaning of 35 U.S.C. § 112, first paragraph. Thus, none of Exhibits 4-7 nor their combination can convince that the application provides an enabling disclosure.

(b) Section 6 of the declaration is not convincing. First, the discussion of potential toxic effects is not relevant because the rejection is not based on the existence of potential toxic effects. Second, declarant offers his opinion as to why researchers did not publish *in vivo* antisense results before the early 1990s (about ten years after the effective filing date of the instant application). These reasons are merely declarant's opinion which opinion is supported only by general views as to the academic research environment and the corporate research environment. Without some factual information, these opinions and general observations of only one individual cannot convince that these reasons were the reason for the failure of any and all groups of researchers to publish an account of *in vivo* antisense working. It is reiterated here that this has been an active field of research since its inception (for example, see the numerous references cited in Rojanasakul). Declarant has not established that he has any special knowledge that puts him in a position to speak for all academic scientists in the field regarding the reasons for such non-publication. Declarant's speculations regarding the reasons for lack of publication by academics are not convincing.

(c) Similarly to the discussion in (b) immediately above, declarant has not established that he is in a position to speak for all pharmaceutical companies in connection with their strategies for pursuing or not pursuing research in the filed of antisense at the time in question (section 7 of the declaration). Anecdotes and generalizations cannot substitute for fact in an attempt to convince one that the instant application contains an enabling disclosure within the meaning of 35 U.S.C. § 112, first paragraph.

Applicant's arguments (paper no. 80, pages 10-25) are not convincing for reasons given hereinabove.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James Martinell whose telephone number is (703) 308-0296. The fax phone number for Examiner Martinell's desktop workstation is (703) 746-5162. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be e-mailed to james.martinell@uspto.gov. Since e-mail communications may not be secure, it is suggested that information in such requests be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (703) 305-4028. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

James Martinell, Ph.D.
Primary Examiner
Art Unit 1631